SnapShot: Organizational Principles of the Postsynaptic Proteome

Neuron

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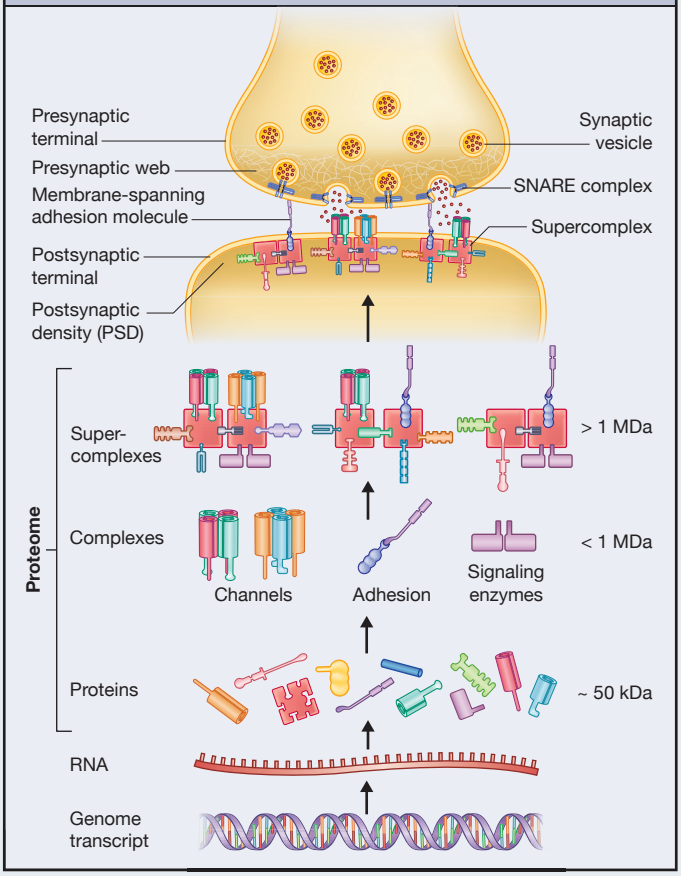
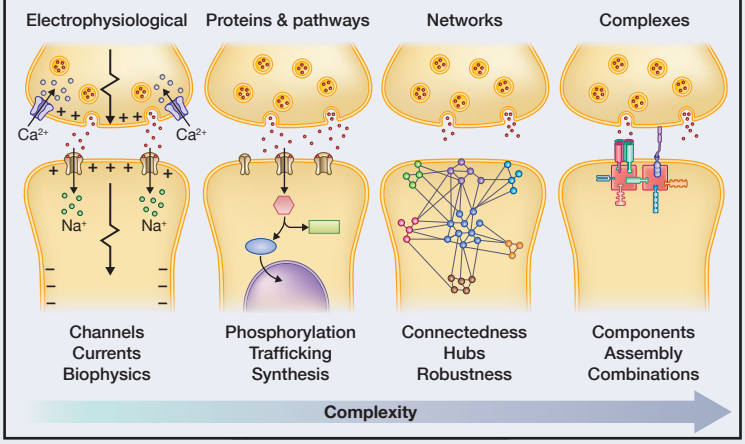
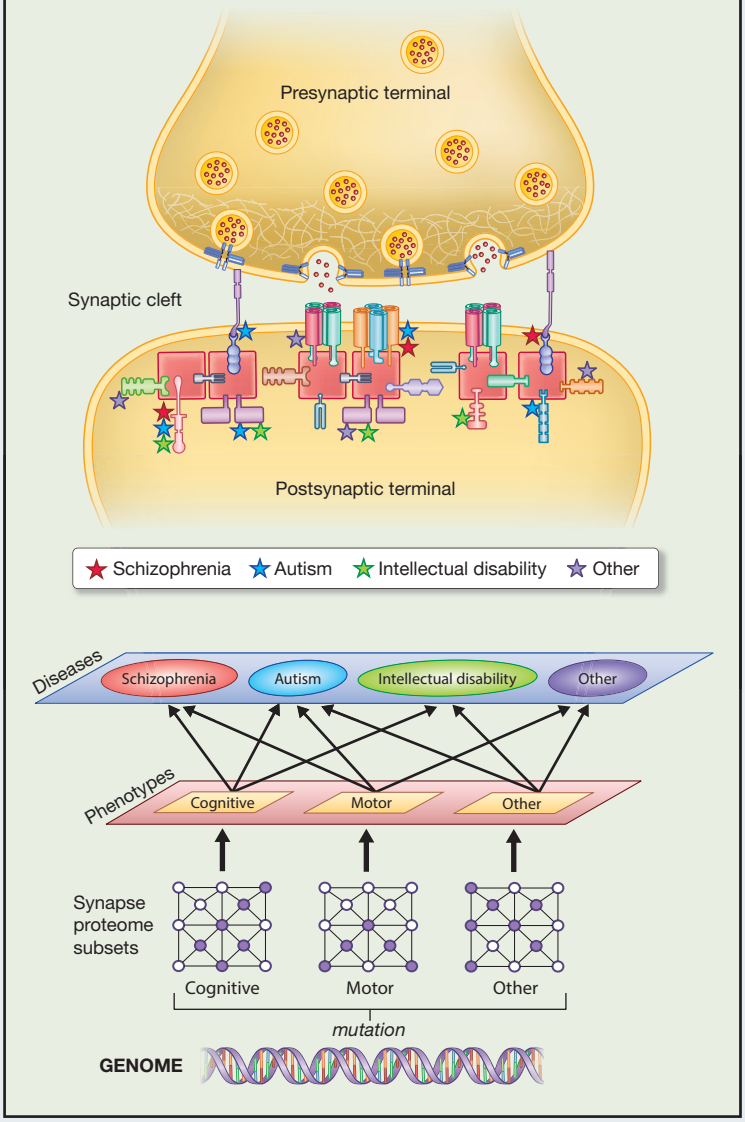
Molecular hierarchy: genes to supercomplexes



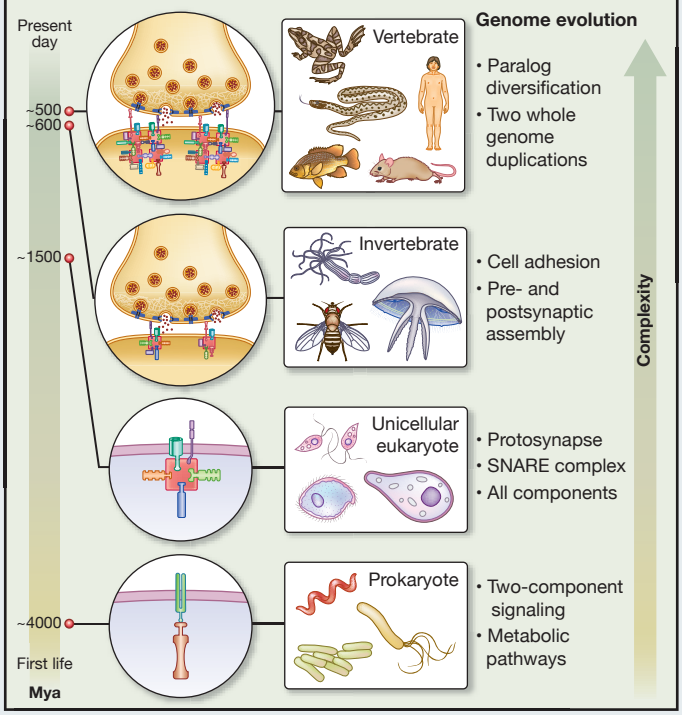
Conceptual frameworks



Synaptopathy



Origins and evolution of synapse proteomes



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Synapses of the central nervous system were first seen with light microscopes in the 19th century but only in the last decade has the extent of the protein machinery within synapses—the synapse proteome—been documented. The postsynaptic proteome of central synapses of humans and other mammals comprises ~1500 protein components (Collins et al., 2006; Bayés et al., 2011). Fewer than 10% are ion channels and receptors and the majority are a diverse range of signaling, structural, and metabolic proteins. The general principles underlying their physical and functional organization are now beginning to emerge and are presented in this SnapShot.

Conceptual Frameworks

Different experimental approaches probe the molecular complexity of the postsynaptic proteome to different extents. These approaches can be classified into four conceptual frameworks (key characteristics in text below each synapse). Electrophysiological studies primarily capture the function of channels and receptors, representing a small fraction of the proteome. Studies of Proteins and Pathways typically study a handful of proteins through perturbations or studies of phosphorylation and evaluate them in the context of a particular downstream phenotype. This view does not reflect the extensive cross-talk and interactions of most proteins, which is better studied in Network approaches. Networks use systems biology representations of large fractions or all of the proteome. For example, phosphoproteomic studies of the neurotransmitter receptor signaling shows that hundreds of phosphorylation sites on many proteins are simultaneously regulated (Coba et al., 2009). Network representations do not directly equate to the physical structure of proteins or their assembly into 3D multiprotein complexes. The Complexes framework describes how sets of proteins are assembled into discrete physical entities that can be biochemically separated and act as molecular machines with specialized functions.

Molecular Hierarchy

The postsynaptic proteome is composed of proteins organized into a hierarchy of protein structures—individual proteins, simple complexes, and supercomplexes—encoded by the genome and transcriptome. Prototypical examples of simple synaptic complexes are tetrameric ion channels or trimeric SNARE complexes, less than 1 MDa in size. Supercomplexes are higher-molecular-weight structures (>1 MDa) that can be assemblies of two or more simple complexes. For example, NMDA receptor complexes bound to scaffold protein complexes and adhesion protein complexes can form supercomplexes (Husi et al., 2000). Different types of complexes and supercomplexes are defined by their combinations of component proteins and the differential distribution of these types into different synapses underpins synapse diversity.

Origins and Evolution of Synapse Proteomes

Three key aspects of brain evolution have been revealed by studies of synapse proteome evolution (Ryan and Grant, 2009; Emes and Grant, 2012): (1) the origin of the neurotransmitter receptor sensing mechanisms arose in the earliest prokaryotes and was followed later in unicellular eukaryotes with sophisticated supercomplexes, (2) a major expansion in synapse proteome complexity occurred in the vertebrate lineage ~550 million years ago generated by whole-genome duplication events, and (3) constraint by purifying selection conserved synapse protein sequence and cognitive components in humans, mice, and other mammals since they evolved from their common ancestor in the last ~90 million years (Bayés et al., 2011; Nithianantharajah et al., 2013).

Synaptopathy

Synaptic disease—known as Synaptopathy—is now recognized as a major cause of brain disease. Mutations in over 200 genes result in disruption to the postsynaptic proteome causing over 130 brain diseases (Bayés et al., 2011). These include common and rare psychiatric, neurological, and developmental disorders. The figure illustrates how different mutations can converge on specific protein subsets of the postsynaptic proteome, such as those that control particular phenotypes (e.g., cognitive and motor functions) and that these phenotypes are the building blocks of different diseases. The convergence of multiple mutations and multiple diseases (such as schizophrenia, autism, and intellectual disability) on the same proteins or the same supercomplexes demonstrates a common synaptopathological etiology to these diseases.

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